

PATENT COOPERATION TREATY

PCT
NOTIFICATION OF ELECTION
(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing: 15 March 2001 (15.03.01)	To: Commissioner US Department of Commerce United States Patent and Trademark Office, PCT 2011 South Clark Place Room CP2/5C24 Arlington, VA 22202 ETATS-UNIS D'AMERIQUE in its capacity as elected Office
International application No.: PCT/US00/24713	Applicant's or agent's file reference: 7770/JB
International filing date: 08 September 2000 (08.09.00)	Priority date: 10 September 1999 (10.09.99)
Applicant: UNDERINER, Todd, Laurence et al	

1. The designated Office is hereby notified of its election made:

in the demand filed with the International preliminary Examining Authority on:
02 January 2001 (02.01.01)

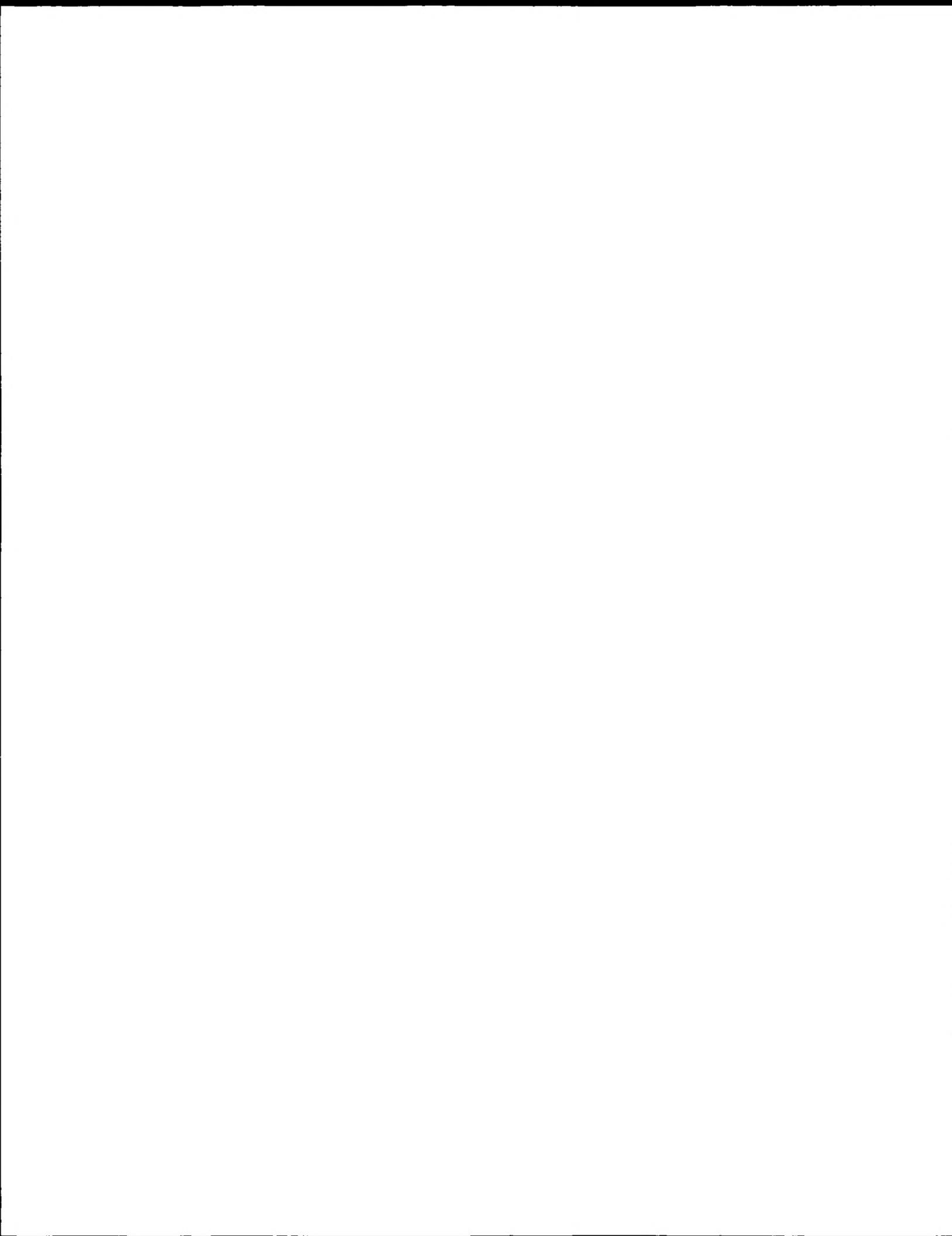
in a notice effecting later election filed with the International Bureau on:

2. The election was

was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer: J. Zahra Telephone No.: (41-22) 338.83.38
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(72) Inventors; and

(75) Inventors/Applicants (for US only): UNDERINER, Todd, Laurence [US/US]; 6262 Seiler Drive, Cincinnati, OH 45239 (US). OSBORNE, Scott, Edward [US/US]; 7071 Wilhelmina Drive, Middletown, OH 45044 (US). BATES, Timothy [US/US]; 1589 Forester Drive, Cincinnati, OH 45240 (US). GARRETT, Garry, Steven [US/US]; 1585 Parliament Court, Fairfield, OH 45014 (US). FOSSUM, Renae, Dianna [US/US]; 501 South Main Street, Middletown, OH 45044 (US).

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(81) Designated States (national): AE, AG, AL, AM, AT, AT (utility model), AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, CZ (utility model), DE, DE (utility model), DK, DK (utility model), DM, DZ, EE, EE (utility model), ES, FI, FI (utility model), GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KR (utility model), KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (utility model), SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

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Published:

— Without international search report and to be republished upon receipt of that report.

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

A2

WO 01/18181

(54) Title: ENZYME INHIBITORS

(57) Abstract: The present invention relates to polymer conjugates which inhibit protease or lipase enzyme, said polymer conjugates comprising a polymer component bonded to an enzyme inhibitor component having an acyl unit capable of inhibiting the activity of more than one protease or lipase enzymes, wherein said inhibitor component is directly bonded to said polymer component or is bonded by a linking unit, said linking unit capable of modulating the interaction of a target enzyme and said inhibitor component wherein said polymer component remains bonded to said inhibitor component after said acyl unit interacts with said target enzyme.



INTERNATIONAL SEARCH REPORT

International application No
PCT/US 01/24713

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K47/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, CHEM ABS Data, EMBASE, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	WO 99 34786 A (GELTEX PHARMA INC) 15 July 1999 (1999-07-15) page 6 page 10 page 36 -page 37; claims 5,6; examples 87,88 ---	1-13
P, X	WO 99 45974 A (UNDERINER TODD LAURENCE ;BATES TIMOTHY (US); MCIVER JOHN MCMILLAN) 16 September 1999 (1999-09-16) abstract; examples 2-4 page 10, line 30 -page 11, line 6; claim 17 page 5, line 5-10 --- -/-	1-13

Further documents are listed in the continuation of box C

Patent family members are listed in annex

Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority, claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

24 July 2001

Date of mailing of the international search report

31/07/2001

Name and mailing address of the ISA

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Gonzalez Ramon, N



INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 0/24713

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, P	WO 99 45973 A (OSBORNE SCOTT EDWARD ; PROCTER & GAMBLE (US); ROE DONALD CARROLL (U) 16 September 1999 (1999-09-16) page 9, paragraph 2 page 10 ---	1-13
P, X	WO 99 46316 A (PROCTER & GAMBLE) 16 September 1999 (1999-09-16) abstract page 21 -page 25; examples 15-17 examples A,C-F ---	1-13
E	WO 01 17501 A (UNDERINER TODD LAURENCE ; BATES TIMOTHY (US); PROCTER & GAMBLE (US)) 15 March 2001 (2001-03-15) abstract; claims 1,14,16,17 page 25; examples 1-3 ---	1-13
A	JARVEST R L ET AL: "Potent selective thienoxazinone inhibitors of herpes proteases" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, GB, OXFORD, vol. 7, no. 13, 8 July 1997 (1997-07-08), pages 1733-1738, XP004136290 ISSN: 0960-894X abstract; examples 1,2 ---	1-13
X	TAKERKART G ET AL: "PREPARATION AND PROPERTIES OF ORGANOPHILIC TRYPSIN MACRO-INHIBITORS DIAMIDINO-ALPHA,OMEGA-DIPHENYLCARBAMYL-POLY(ETHYLENE GLYCOL)" FEBS LETTERS, XX, XX, vol. 42, no. 2, June 1974 (1974-06), pages 214-220, XP000870353 ISSN: 0014-5793 page 214, paragraph 1 ---	1-13
A	PINTO I L ET AL: "Inhibition of human cytomegalovirus protease by enedione derivatives of thieno'2,3-d'oxazinones through a novel dual acylation/alkylation mechanism" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, GB, OXFORD, vol. 9, no. 3, 8 February 1999 (1999-02-08), pages 449-452, XP004157245 ISSN: 0960-894X abstract -----	1-13



FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-13

Present claims 1-13 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Moreover the claims relate to compounds defined by reference to desirable characteristics or properties, namely "enzyme inhibitor component", "a linking unit capable of modulating the interaction between a target enzyme and inhibitor component", "template unit" etc. The claims cover all compounds having these characteristics or properties, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds described and prepared in the examples (v.e. MPEG or PEG derived conjugates) with due regard to the general idea underlying the present application.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.



INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 01/24713

Patent document cited in search report	Publication date	Patent family member(s)			Publication date
WO 9934786	A 15-07-1999	AU 2105699	A	26-07-1999	
		BR 9907233	A	17-10-2000	
		CN 1287489	T	14-03-2001	
		EP 1043982	A	18-10-2000	
		NO 20003511	A	07-09-2000	
WO 9945974	A 16-09-1999	AU 3079799	A	27-09-1999	
		BR 9908564	A	05-12-2000	
		CN 1300224	T	20-06-2001	
		EP 1061963	A	27-12-2000	
WO 9945973	A 16-09-1999	AU 3079599	A	27-09-1999	
		BR 9908565	A	12-12-2000	
		CN 1300223	T	20-06-2001	
		EP 1061962	A	27-12-2000	
		TR 200002601	T	21-12-2000	
WO 9946316	A 16-09-1999	US 6066673	A	23-05-2000	
		AU 2903799	A	27-09-1999	
		CN 1300303	T	20-06-2001	
		EP 1062264	A	27-12-2000	
		NO 20004550	A	10-11-2000	
		US 6211186	B	03-04-2001	
WO 0117501	A 15-03-2001	AU 7127100	A	10-04-2001	

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 7770/JB	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/US 00/24713	International filing date (day/month/year) 08/09/2000	(Earliest) Priority Date (day/month/year) 10/09/1999
Applicant THE PROCTER & GAMBLE COMPANY		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

contained in the international application in written form.

filed together with the international application in computer readable form.

furnished subsequently to this Authority in written form.

furnished subsequently to this Authority in computer readable form.

the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. **Certain claims were found unsearchable** (See Box I).

3. **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

the text is approved as submitted by the applicant.

the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

the text is approved as submitted by the applicant.

the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

as suggested by the applicant.

because the applicant failed to suggest a figure.

because this figure better characterizes the invention.

None of the figures.



INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70) 12

Applicant's or agent's file reference 7770/JB	FOR FURTHER ACTION		See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US00/24713	International filing date (day/month/year) 08/09/2000	Priority date (day/month/year) 10/09/1999	
International Patent Classification (IPC) or national classification and IPC A61K47/48			
Applicant THE PROCTER & GAMBLE COMPANY			

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 14 sheets, including this cover sheet.
 - This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I Basis of the report
- II Priority
- III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV Lack of unity of invention
- V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI Certain documents cited
- VII Certain defects in the international application
- VIII Certain observations on the international application

Date of submission of the demand 02/01/2001	Date of completion of this report 18.12.2001
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Lopez Garcia, F Telephone No. +49 89 2399 2171





INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/24713

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, pages:

1-47 as originally filed

Claims, No.:

1-13 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- the language of publication of the international application (under Rule 48.3(b)).
- the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- contained in the international application in written form.
- filed together with the international application in computer readable form.
- furnished subsequently to this Authority in written form.
- furnished subsequently to this Authority in computer readable form.
- The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- the description, pages:
- the claims, Nos.:
- the drawings, sheets:

5. This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):



INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/24713

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:
see separate sheet

II. Priority

1. This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:
 - copy of the earlier application whose priority has been claimed.
 - translation of the earlier application whose priority has been claimed.

2. This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:
see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- the entire international application.
- claims Nos. 1-13(insofar as they have not been searched).

because:

- the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):
- the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- no international search report has been established for the said claims Nos. 1-13(insofar as they have not been searched).



INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/24713

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

- the written form has not been furnished or does not comply with the standard.
- the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims 1-13 (partially)
	No: Claims 1-13 (partially)
Inventive step (IS)	Yes: Claims 1-13 (partially)
	No: Claims 1-13 (partially)
Industrial applicability (IA)	Yes: Claims 1-13
	No: Claims

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet



Re Item I

Basis of the report

1. A partial search has been carried out (see ISA 210, Box I.2). Only those compounds/compositions described and prepared in the examples 1-7 (MPEG or PEG derived conjugates) have been searched. Therefore, the IPEA will carry out a preliminary examination only on that matter which has been searched, ie the compounds of claims 1-13, insofar as the compounds of the examples 1-7 are concerned. The polysaccharide polymer conjugates (claims 3 [Poly]ii, 7ii, 12ii) and the polyamine polymer conjugates (claims 3 [Poly]iii, 7iii, 12iii) as well as the polyalkylene oxide polymer conjugates different from those described and prepared in the examples 1-7 (MPEG or PEG derived conjugates) have not been searched.

Re Item II

Priority

1. Priority seems to be only partially validly claimed:

Claim 1: Support, in the priority document, is not found for an acyl unit capable of inhibiting the activity of one protease or lipase enzymes (cf. with claim 1 of priority document).

Claim 2: It is supported only in the case of $[[[Mod]-O-C(O)]_w-T]_y-[(L)_z-[Poly]]_y$ (cf. with formula of p. 5 of priority document).

Claim 3: Support is found only for those embodiments found in the priority document at p. 9, l. 10-p. 12, l. 7 of the priority document:

(i) is supported in the priority document only when:

- a) D,E,F,G=CH
- b) D,E,F=CH and G=N
- c) D,E=CH, F=N, G=CH
- d) D,F,G=CH, E=N
- e) E,F,G=CH, D=N



- f) E,F=CH, D,G=N
- g) D,F=CH, E,G=N
- h) E,G=CH, D,F=N

(ii) is supported in the priority document only when D,E,F,G=CH R'=H.

(iii) is supported in the priority document only when

- a) E,F,G=CH2
- b) E=S, F,G=CH2

(iv) is supported in the priority document only when:

- a) E=S, F,G=CH
- b) E=S, F=CR, G=N
- c) E=NR, F=CR, G=N

(v) is supported in the priority document only when:

- a) E=CH, F=CH, G=S
- b) E=N, F=CR, G=S
- c) E=N, F=CR, G=NR

(vi) is supported in the priority document only when D,E,F,G=CH

(vii) is NOT supported.

(viii) is NOT supported.

(ix) is NOT supported.

(x) is supported.

Support is not found for R8 (xviii, xix, xx, xxiii, xxiv, xxv), for R9 (i, xv, xvi), for L (xix, xx, xxiv, xxv, and xxvi) (cf. with definition of said groups in both priority, at p. 14-23- p. 18, l. 11, and the claim).

Claim 4: Support is found for i when X=O (cf. with formula of p. 5 or the priority



document), but ii, iii and iv are not found in the priority document.

Claim 5: Support is not found in the priority documents for R8 (xviii, xix, xx, xxiii, xxiv, xxv), for R9 (i, xv, xvi). See claim 3, above.

Claim 9: Support is found for compositions having from 0.1% of the conjugate but not for those having from 0.01% (cf. with p. 33, I. 5 of the priority document).

Claim 10: Support is not found in the priority documents for R8 (xviii, xix, xx, xxiii, xxiv, xxv), for R9 (i, xv, xvi). See claim 3, above.

Claim 13: Not support is found for the specific embodiments of claim 13.

The compounds of the examples 1-3 cannot be found in the priority document.

The documents D2-D4 are therefore prior art for the subject-matter for which priority is not validly claimed.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. A partial search has been carried out (see ISA 210, Box I.2). Only those compounds/compositions described and prepared in the examples 1-7 (MPEG or PEG derived conjugates) have been searched. Therefore, the IPEA will carry out a preliminary examination only on that matter which has been searched, ie the compounds of claims 1-13, insofar as compounds of the examples 1-7 are concerned. The polysaccharide polymer conjugates (claims 3 [Poly]ii, 7ii, 12ii) and the polyamine polymer conjugates (claims 3 [Poly]iii, 7iii, 12iii) as well as the polyalkylene oxide polymer conjugates different from those described and prepared in the examples 1-7 (MPEG or PEG derived conjugates) have not been searched. Therefore, not opinion will be given for conjugates encompassing a polysaccharide, a polyamine polymer and polyalkylene oxide polymer conjugates different from those described and prepared in the examples 1-7.



2. On the other hand, in the case of a complete search, the application would have lacked unity (Rule 13 PCT).

The idea of providing a composition comprising a conjugate of a polymer with a protease inhibitor is known in the art (see D1 and D7, below). Therefore, this cannot be the common linking feature of the different conjugates proposed in the application:

- I. Polyalkylene oxide polymer conjugates (claims 1-12 partially, 13 complete).
- II. Polysaccharide polymer conjugates (claims 1-12 partially)
- III. Polyamine polymer conjugates (claims 1-12 partially).

In absence of any other "special technical feature" in the sense of Rule 13.2 PCT the application is considered to lack unity, in the sense of Rule 13 PCT.

Therefore, the searched-matter belongs to the first invention found in the application.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents:

- D1: WO 99 34786 A
- D2: WO 99 45974 A 16 September 1999
- D3: WO 99 45973 A 16 September 1999
- D4: WO 99 46316 A 16 September 1999
- D5: WO 01 17501 A 15 March 2001
- D6: JARVEST BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 7, 1997, p. 1733-1738.
- D7: TAKERKART FEBS LETTERS, vol. 42, 1974, p. 214-220.
- D8: PINTO BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 9, 8



February 1999, p. 449-452.

D9: Surfactants in cosmetics, 2nd Edition (1997), p. 23, Ed. Rieger & Rhein, Marcel Dekker, Inc. New York, Basel, Hong Kong.

2. The searched subject-matter of the present application has been restricted to the compounds of examples 1-7, ie to the subject-matter of claims 1-13 (**partially**). The object of the application is the treatment of skin irritation.

Thus the subject-matter examined comprises exclusively the following compounds: 2-(MPEG 5000)-5-methyl-4H-3,1-benzoxazin-4-one (examples 1 and 2); bis-2-(PEG 4000)-5-methyl-4H-3,1-benzoxazin-4-one (example 3); 2-N-(PEG 5000) amino-4H-3,1-benzoxazin-4-one (example 4); N-4-(7-guanidinyl-4H-3,1-benzoxazin-4-one-2-yl)phenylene-N'-PEG 5000 urea (example 5); 2-PEG 5000-8-methyl-4H-3,1-benzoxazin-4-ona (example 6); 2-PEG 5000-[2,3-d]thieno[1,3]oxazin-4-one (example 7).

3. Novelty of the searched subject-matter

None of the documents D1-D4, D6-D8 disclose the conjugates 2-(MPEG 5000)-5-methyl-4H-3,1-benzoxazin-4-one (examples 1 and 2); bis-2-(PEG 4000)-5-methyl-4H-3,1-benzoxazin-4-one (example 3); 2-N-(PEG 5000) amino-4H-3,1-benzoxazin-4-one (example 4); N-4-(7-guanidinyl-4H-3,1-benzoxazin-4-one-2-yl)phenylene-N'-PEG 5000 urea (example 5); 2-PEG 5000-5-methyl-4H-3,1-benzoxazin-4-ona (example 6); 2-PEG 5000-[2,3-d]thieno[1,3]oxazin-4-one (example 7).

D5 is not prior art.

Therefore, the subject-matter of claims 1-13 (partially) seems to be novel (Art. 33(2) PCT).

4. Inventive step of the searched subject-matter

D4, which is considered the closest prior art for those compound for which priority is not validly claimed, discloses the compounds of formula I useful for skin care



(see abstract). Said compounds comprise a guanidino group which is an enzyme inhibitor (p. 4, l. 7-8), an aromatic group and a poly(alkylene oxide) moiety which facilitates penetration into the sebum (p. 3, l. 36-37).

The difference between the application and D4 is that the aromatic group is either benzoxazinones or thienoxazinones.

The technical problem is the provision of further enzyme inhibitors.

Benzoxazinones and thienoxazinones are known protease inhibitors (D6, compounds 1 and 2 and D8, compounds 1, 5-16). It would be obvious for the skilled person to substitute the aromatic group of the compounds of formula I of D4 for benzoxazinones and thienoxazinones of D6 and D8 when providing further enzyme inhibitors for skin care, since said heterocycles are also protease inhibitors.

On the other hand, it would be also obvious for the skilled person to combine the benzoxazinones and thienoxazinones of D6 and D8 with poly(alkylene oxide), since it facilitates the penetration into the sebum (D4, p. 3, l. 36-37).

Therefore, the subject-matter of claims 1-13 (**partially**) is not inventive (**Art. 33(3) PCT**), insofar as their priority is not validly claimed.

5. Novelty of non-searched subject-matter

Although the search has been restricted to those compounds/compositions which can be found in the examples 1-7, the IPEA wants to draw the Applicant's attention to the content of the following documents which destroy the novelty of claims 1-13 due to its broad scope:

- 5.1. D1 discloses method for treatment of human obesity by using lipase inhibiting polymers (see title). Said conjugates comprise a polymer part (p. 9, l. 7-p. 12, l. 16, specially polymers of formula IX at p. 10) and a lipase inhibitor. Among the lipase inhibitors (at p. 6 and at p. 7 IV and V) have an acyl group or a precursor of said acyl groups (as said at p. 3, l. 24-27 of the present application). PLURONIC



is a trademark for polyethyleneglycol-polypropylene glycol copolymers. The content of the examples 84 (p. 30), 85 (p. 30), 86 (p. 31), 87 (p. 35) and 88 (p. 37) destroys the novelty of claims 1, 2, 4, 6-10, 12, 13 (Art. 33(2) PCT).

- 5.2. D2 discloses skin care compositions containing an enzyme inhibitor in absorbent articles (see abstract). Said compositions do not fall within the scope of the present application for which priority has not been validly claimed. Therefore, the subject-matter of claims 1-13 is novel over D2 (Art.33(2) PCT).
- 5.3. D3 discloses a disposable absorbent article having a skin care compositions containing an enzyme inhibitor (see abstract). Said compositions do not fall within the scope of the present application for which priority has not been validly claimed. Therefore, the subject-matter of claims 1-13 is novel over D3 (Art.33(2) PCT).
- 5.4. D4 discloses the compounds of formula I which are useful for skin care (see abstract). Compounds at p. 21-25 and those of examples 1-17 appears that fall within the subject-matter of claims 1, 2, 4, 6, 7, 8, 9, 13 for which the priority seems to be, partially, not validly claimed (see Priority, above). Therefore, said claims are not novel (Art. 33(2) PCT).
- 5.5. D5 is not prior art at present.
- 5.6. D6 discloses the thienoxazinone inhibitors of herpes proteases (see abstract, compounds 1 and 2 (p. 1733) and tables 1, 2, and 3 at p. 1736-1737). R groups can be considered as "a polymer unit". Therefore, the subject-matter of claims 1-6, 8-11 is not novel over the content of D6 (Art.33(2) PCT).
- 5.7. D7 discloses the preparation of conjugates comprising a polymer (PEG) and an enzyme inhibitor (PAB) (see 2.1 at p. 214). Therefore, the subject-matter of claims 1, 2, 7, 8, 9, 12 and 13 is not novel (Art. 33(2) PCT).
- 5.8. D8 discloses the thienooxazinones 5-16 which are protease inhibitors (see p. 449, last paragraph and Table 1). R group can be considered as "a polymer unit". Therefore, the subject-matter of claims 1-6, 8-11 is not novel over the content of



D8 (Art.33(2) PCT).

5.9. The Applicant's attention is drawn to the fact that, **for example**, the vitamins K or B2 which contain an "acyl group" precursor and a polymeric chain, or the polyethoxylated esters of fatty acids (see D9), fall within the scope of claims 1, 2, 4 and 7 and their compositions may fall within the scope of claims 8-10, 12 and 13, since said compounds fall within the formula of claim 2.

Re Item VI

Certain documents cited

Certain published documents (Rule 70.10)

Application No Patent No	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
WO9945974	16.09.99	11.03.99	12.03.98
WO9945973	16.09.99	11.03.99	12.03.98
WO9946316	16.09.99	11.03.99	12.03.98
WO0117501	15.03.01	08.09.00	10.09.99
WO0117564	15.03.01	08.09.00	10.09.99
WO0117565	15.03.01	08.09.00	10.09.99

The Applicant's attention is drawn to the content of the **PCT Guidelines, IV 6.3** in relation with the subject-matter of the present application which overlaps with the content of the International Applications WO0117501, WO0117564 and WO0117565.

Re Item VII

Certain defects in the international application

1. The dependence of claim 4 upon claim 4 as well as the dependence of claim 11 upon claim 11 has not any sense.
2. The dependence of claim 6 upon claim has not sense. Moreover, R appears for the first time in claim 3 and is not present in claim 4.



3. Claim 10 refers to the compounds of claims 8 or 9 which are compositions.
4. R19 of claim 13 is not found in the formulas of said claim.
5. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1, D6, D7 and D8 is not mentioned in the description, nor are these documents identified therein.

Re Item VIII

Certain observations on the international application

1. Claim 1 does not meet the requirements of Art. 6 PCT. It relates to a conjugate, wherein the structural constituents have been defined by their function/result-to-be-achieved ("linking unit", "enzyme inhibitor", "capable of", etc.) These expressions cannot serve for defining without ambiguity the contribution to the art, since none of these terms has a clear technical meaning. Better technical features, which will help to define the scope of said claim and to obtain the result or effect desired, are obtained by identifying the polymer component, the inhibitor component and the acyl unit. On the other hand, expressions like "inhibitor component" or "polymer component" are unclear, since it is not known whether they refer to a unit or a part of said inhibitor or polymer. For instance, a **proton** atom can be considered as such component.

The subject-matter of claim 1 is so broadly defined that it would be an undue burden for the skilled person to determine which are the technical features of the present invention.

2. Claim 2 does not meet the requirement of Art. 6 PCT for the following reasons: a) An acyl group is R-C(O)-. Many of the possible combinations of the formula of said claim are not acyl groups. It appears that **any** compound containing a double bond falls within the definition of acyl group. b) The expression "mixtures thereof" of option h) together with its repetitions in several of the other options of other claims is unusual in the context of defining radicals and groups present in a chemical structure as pool of options and chemically misleading. The expression "polymer unit" is unclear, since it is not known whether this is intended to include



monomeric units and which is its chemical nature or its size. "Template unit" is also unclear, since it is not known what is intended with the words template or unit.

3. Claims 3 does not meet the requirements of Art. 6 PCT since a group [Mod]-XC(O)-T is not present in claims 1 or 2. Option o) is chemically absurd, since there is only one group R linked to a carbon atom of a phenyl moiety and it cannot be that two "R units" are linked to the same carbon atom. The expression "carbonyl unit equivalent" lacks clarity, since it is not known if it refers to chemical or biological equivalence (these objections are also applicable to claims 5, option o) and 11 option o).
4. Claim 8 does not meet the requirements of Art. 6 PCT. In particular, "polymer component" or "enzyme inhibiting component" are unclear expressions, since it is not known whether they are intending to portions of said polymers/enzymes (an H atom) or to monomers and which is its chemical nature or its size. The expression "enzyme directing" has not a recognized meaning and it is unclear what is intended with it. The "polymer component", the "enzyme inhibiting component", "linking unit" and the "acyl unit" should be defined in order to obtain the result/effect expected, ie inhibit protease or lipase, or interact with said enzymes, or capable of interacting with said enzymes.
5. Objections to claim 9 can be raised as for claims 1 and 8.
6. The application lacks conciseness (Art. 6 PCT). The extensive definition of the radicals of claim 11 can refer to those of claim 5. The extensive definition of the radical R of claims 5, Poly of claim 7, R of claim 11 and Poly of claim 12 can refer to those of claim 3.



INTERNATIONAL SEARCH REPORT

I. National/International No

PCT/US 99/05314

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 6 C08G65/48 A61K31/155 C07C279/18 C07C257/18 C07C257/14
 A61K31/77

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC 6 C07C A61K C08G A61L C11D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	TAKERKART, GEORGES ET AL: "Preparation and properties of organophilic trypsin macroinhibitors. Diamidino-.alpha.,.omega.-diphenylcarbamyl polyethylene glycol" FEBS (FED. EUR. BIOCHEM. SOC.) LETT. (1974), 42(2), 214-17 , XP000870353 page 214 ---	1-10
A	EP 0 658 585 A (BEHRINGWERKE AG) 21 June 1995 (1995-06-21) claims; example 1 ---	1-10
A	US 4 556 560 A (BUCKINGHAM KENT W) 3 December 1985 (1985-12-03) page 1-4 -----	10

Further documents are listed in the continuation of box C.

Patent family members are listed in annex

Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority, claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

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Information on patent family members

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			CA 2137748 A		11-06-1995
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US 4556560	A	03-12-1985	CA 1225026 A		04-08-1987
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			JP 2533471 B		11-09-1996
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